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# *FAX Transmission Sheet*

***Official***

December 18, 2007

Our Docket No.: 868_012

To: Magdalen Greenlief Fax No.: (571) 273-0125

From: Stephen P. Burr Fax No.: (315) 233-8320

Re: In re the Application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

Serial No.: 10/587,320 Art Unit: 4173

Date Filed: May 10, 2007 Conf. No. 4731

Title: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

I hereby certify that the following page(s) **including this cover** is/are being transmitted via facsimile to Magdalen Greenlief at (571) 273-0125 at the Patent and Trademark Office on ***December 18, 2007***:

| | | Paper | Index of Pages | # of Pages |
|---|---|---|---|---|
| 1. | | This Cover Page | | 1 |
| 2. | | Form PTO/SB/20 (Request for Participation in the PPH Pilot Program Between the (1) JPO or (2) UKIPO, and the USPTO | | 2 |
| 3. | I.(a)(i)* | JPO Notification of Reasons for Refusal | 1-2 | |
| | | Translator's Certificate | 3-3 | |
| | | English Translation | 4-5 | 5 |
| 4. | I.(a)(ii)* | JPO Notice of Allowance | 1-1 | |
| | | Translator's Certificate | 2-2 | |
| | | English Translation | 3-3 | 3 |
| 5. | II.(b)(i)* | Explanation of Circumstances Concerning Accelerated Examination filed 5/15/07 in Japan | 1-14 | |
| | | Translator's Certificate | 15-15 | |
| | | English Translation | 16-38 | 38 |
| 6. | II.(b)(ii)* | Amendment filed 5/14/07 in JP 2005-517502 | 1-3 | |
| | | Translator's Certificate | 4-4 | |
| | | English Translation | 5-7 | 7 |
| 7. | II.(b)(iii)* | Amendment filed 8/3/07 in JP 2005-517502 | 1-3 | |
| | | Translator's Certificate | 4-4 | |
| | | English Translation | 5-7 | 7 |
| 8. | | Copy of Supplemental Information Disclosure Statement filed 12/17/07 | 1-1 | |
| | | Form PTO-1449 | 2-2 | 2 |
| 9. | | Copy of Supplemental Preliminary Amendment filed 12/18/07 | 1-4 | 4 |
| | | | ***Total Pages*** | **69** |

Elizabeth VanAntwerp

Elizabeth A. VanAntwerp

*These headings correspond to the headings on Form PTO/SB/20.

PTO/SB/20 (09-07)
Approved for use through 1 2/31/2008. 0MB 0651-0058
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE


# REQUEST FOR PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM BETWEEN THE (1) JPO OR (2) UKIPO, AND THE USPTO

| | | | |
|---|---|---|---|
| Application No.: | 10/587,320 | First Named Inventor: | Noriaki KATO |
| Filing Date: | May 10, 2007 | Attorney Docket No.: | 868_012 |
| Title of the Invention: | PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY | | |

**THIS REQUEST FOR PARTICIPATION IN THE PPH PILOT PROGRAM MUST BE FAXED TO: THE OFFICE OF THE COMMISSIONER FOR PATENTS AT 571-273-0125 DIRECTED TO THE ATTENTION OF MAGDALEN GREENLIEF**

**APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PPH PILOT PROGRAM.**

The above-identified application validly claims priority under 35 U.S.C. 119(a) and 37 CFR 1.55 to one or more corresponding JPO application(s) or UKIPO application(s).

The ☒ **JPO** ☐ **UKIPO** application number(s) is/are: PCT/JP2005/001187 (Japanese Application No. 2005-517502)

The filing date of the ☒ **JPO** ☐ **UKIPO** application(s) is/are: PCT filing date is January 28, 2005 (National Stage entry date is July 13, 2006)

I. List of Required Documents:

a. **A copy of all JPO office actions (excluding "Decision to Grant a Patent"*) in the above-identified JPO application(s), or a copy of all UKIPO office actions in the above-identified UKIPO application(s).**

☒ Is attached.

☐ Is available via Dossier Access System. Applicant hereby requests that the USPTO obtain these documents via the Dossier Access System.

*It is not necessary to submit a copy of the "Decision to Grant a Patent" and an English translation thereof.

b. **A copy of all claims which were determined to be patentable by the JPO in the above-identified JPO application(s), or a copy of all claims which were determined to be patentable by the UKIPO in the above-identified UKIPO application(s).**

☒ Is attached.

☐ Is available via Dossier Access System. Applicant hereby requests that the USPTO obtain these documents via the Dossier Access System.

c. **English translations (where applicable) of the documents in a. and b. above along with a statement that the English translations are accurate are attached.**

**Information disclosure statement listing the documents cited in the JPO office actions or UKIPO office actions is attached.**

Copies of all documents are attached except for U.S. patents or U.S. patent application publications.

PTO/SB/20 (09-07)
Approved for use through 12/31/2008. OMB 0651-0056
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE


**REQUEST FOR PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM BETWEEN THE (1) JPO OR (2) UKIPO, AND THE USPTO**
(continued)

| Application No.: | 10/587,320 | First Named Inventor: | Noriaki KATO |
|---|---|---|---|

**II. Claims Correspondence Table:**

| Claims in US Application | Patentable Claims in JP/UKIPO Application | Explanation regarding the correspondence |
|---|---|---|
| 10* | 1 | (*as amended on December 18, 2007) |
| 11 | - | there is no claim in JP 2005-517502 that corresponds to claim 11 in USSN 10/587,320 |
| 12 | 2 | |
| 13 | 3 | |
| 14 | 4 | |

**III. All the claims in the U.S. Application sufficiently correspond to the patentable/allowable claims in the JPO or UKIPO application.**

**IV. Payment of Fees:**

The Commissioner is hereby authorized to charge the petition fee under 37 CFR 1.17(h) ($130.00) as required by 37 CFR 1.102(d) to: ☒ Deposit Account No.:50-1446.
☐ Credit Card. Credit Card Payment Form (PTO-2038) is attached.

| Signature | Date December 18, 2007 |
|---|---|
| Name (Print/Typed) Stephen P. Burr | Registration Number 32,970 |

U.S. Patent Application Serial No. 10/587,320

# TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of Amendment on 14th May 2007 is accurate.

Date Nov. 29, 2007

KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

# TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of EXPLANATION OF CIRCUMSTANCES CONCERNING ACCELERATED EXAMINATION on 15th May 2007 is accurate.

Date Nov. 29 2007

KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

# TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of NOTIFICATION OF REASONS FOR REFUSAL on 18th July 2007 is accurate.

Date NOV. 29, 2007

KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

# TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of Amendment on 3rd August 2007 is accurate.

Date Nov. 29, 2007

KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

# TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of NOTIFICATION OF ALLOWANCE on 27th August 2007 is accurate.

Date NOV. 29, 2007

KOBAYASHI Youhei

[Document Name] AMENDMENT

[Reference] P06023SKK

[Filing Date] 14th May 2007

[Address] To the Commissioner, Patent Office

[Case Identification]

[Application Number] Patent Application No. 2005-517502

[Amender]

[Identification Number] 000144577

[Name] SANWA KAGAKU KENKYUSHO CO., LTD.

[Agent]

[Identification Number] 100108280

[Patent Attorney]

[Name] KOBAYASHI Youhei

[Telephone] 0594-27-5515

[Amendment 1]

[Amended Document] CLAIMS

[Amended Item] Whole Document

[Amending Method] Modification

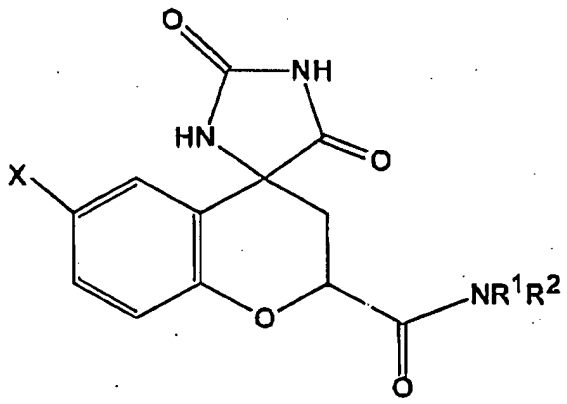
[Amendment Contents]

[Document Name] CLAIMS

[Claim 1]

A prophylactic or therapeutic agent for diabetic maculopathy, comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula 1]



(wherein X represents a halogen or a hydrogen atom, $R^1$ and $R^2$ concurrently or differently represent a hydrogen atom or an optionally substituted C1 to C6 alkyl group, or $R^1$ and $R^2$ together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 2] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

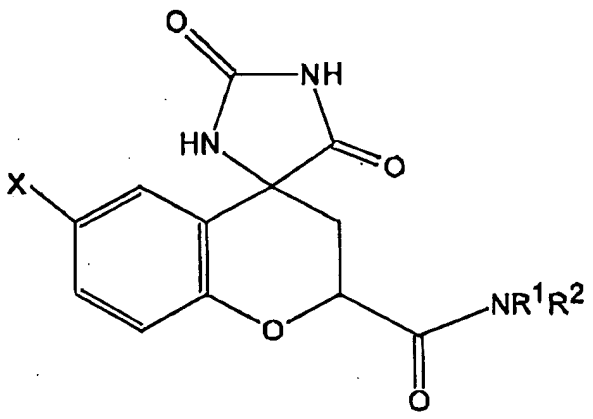
[Claim 3] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use in macular edema or in retinal pigment epitheliopathy in diabetic maculopathy.

[Claim 4] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use as an agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy.

[Claim 5] An agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy,

comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula]

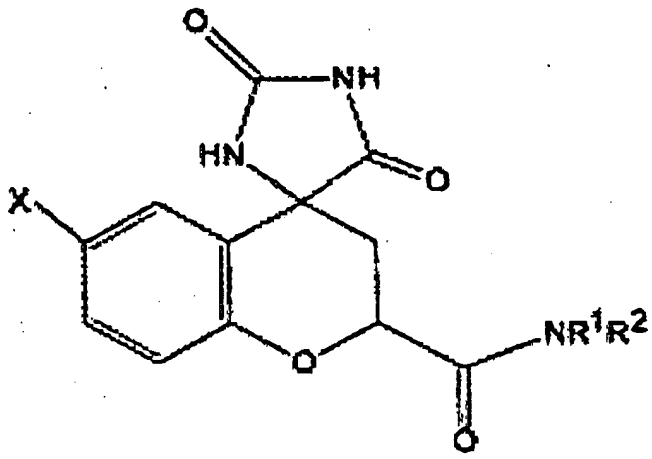



(wherein X represents a halogen or a hydrogen atom, $R^1$ and $R^2$ concurrently or differently represent a hydrogen atom or an optionally substituted C1 to C6 alkyl group, or $R^1$ and $R^2$ together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 6] The agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy, according to claim 5, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

【書類名】　手続補正書
【整理番号】　Ｐ０６０２３ＳＫＫ
【提出日】　平成１９年５月１４日
【あて先】　特許庁長官　殿
【事件の表示】
　【出願番号】　特願２００５－５１７５０２
【補正をする者】
　【識別番号】　０００１４４５７７
　【氏名又は名称】　株式会社　三和化学研究所
【代理人】
　【識別番号】　１００１０８２８０
　【弁理士】
　【氏名又は名称】　小林　洋平
　【電話番号】　０５９４－２７－５５１５
【手続補正１】
　【補正対象書類名】　特許請求の範囲
　【補正対象項目名】　全文
　【補正方法】　変更
　【補正の内容】
　　【書類名】特許請求の範囲
　　【請求項１】一般式
【化１】

II(b)(ii)



（式中Ｘはハロゲン又は水素原子を意味し、$R^1$および$R^2$は、同時にあるいは別々に、水素原子、置換されていてもよいC1-6アルキル基を示すか、又は、$R^1$と$R^2$は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に５～６員の複素環を示す。）

で示される化合物を有効成分とする、糖尿病黄斑症の予防又は治療剤。

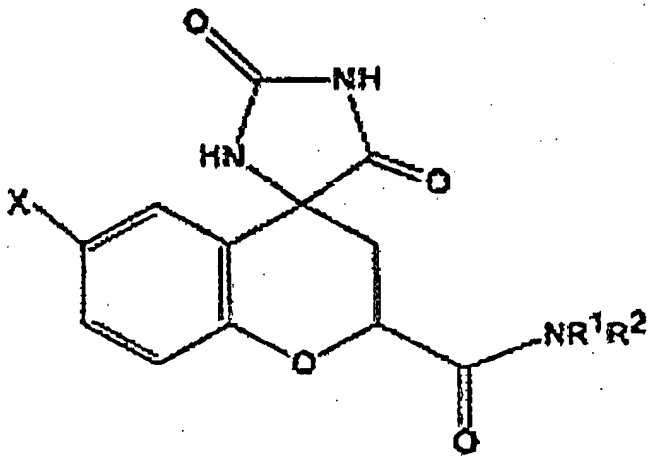
【請求項２】　化合物が(２Ｓ,４Ｓ)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項１に記載の糖尿病黄斑症の予防又は治療剤。

【請求項３】　糖尿病黄斑症における黄斑浮腫又は糖尿病色素上皮症に使用される、請求項１又は２に記載の糖尿病黄斑症の予防又は治療剤。

【請求項４】　糖尿病黄斑症における視力の改善又は低下防止剤として使用される、請求項１又は２に記載の糖尿病黄斑症の予防又は治療剤。

【請求項５】　一般式

【化２】




（式中Ｘはハロゲン又は水素原子を意味し、$R^1$および$R^2$は、同時にあるいは別々に、水素原子、置換されていてもよいC1-6アルキル基を示すか、又は、$R^1$と$R^2$は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に５～６員の複素環を示す。）

で示される化合物を有効成分とする、糖尿病黄斑症における視力の改善又は低下防止剤。

【請求項６】　化合物が(２Ｓ,４Ｓ)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項５に記載の糖尿病黄斑症における視力の改善又は低下防止剤。

[Document Name] EXPLANATION OF CIRCUMSTANCES CONCERNING ACCELERATED EXAMINATION

[Filing Date] 15th May 2007

[Reference] P06023SKK

[Address] To the Commissioner, Patent Office

[Case Identification]

[Application Number] Patent Application No. 2005-517502

[Filer]

[Identification Number] 000144577

[Name] SANWA KAGAKU KENKYUSHO CO., LTD.

[Agent]

[Identification Number] 100108280

[Patent Attorney]

[Name] KOBAYASHI Youhei (Seal)

[Telephone] 0594-27-5515

[Statement about Background of Accelerated Examination]

1. Background

Corresponding patent applications have been filed with the European Patent Office, U.S. Patent and Trademark Office, Chinese Patent Office, Korean Patent Office, Canadian Patent Office and Australian Patent Office.

The European patent application has been assigned with application No. 05704239.2. The U.S. patent application has been assigned with application No. 10/587,320. The Chinese patent application has been assigned with application No. 200580003659.1. The Korean patent application has been assigned with application No. 10-2006-7015812. The Canadian patent application has been assigned with application No. 2554679. The

Australian patent application has been assigned with application No. 2005207906.

2. Disclosure and Comparative Explanation of Prior Art

(1) Document Names

According to an International Preliminary Examination conducted in the original International Patent Application (PCT/JP2005/1187), the following are documents relevant to the present invention:

Document 1: MA Speicher et al., Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging Drugs 2003; 8; 239-250.

Document 2: M Akita et al., Effects of an aldose reductase inhibitor, SNK-860, on the histopathological changes of retinal tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47: 299-304.

Document 3: JP-A-H07-242547

(2) Comparative Explanation

The present invention has been amended by an Amendment filed on 14th May.

(i) The Invention of Claim 1 and Prior Art Documents

Claim 1 is the invention relating to a prophylactic or therapeutic agent for diabetic maculopathy, which contains, as an effective ingredient, a compound represented by the general formula [Chemical Formula 1]. The compound represented by the general formula contains (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide known as SNK-860 and a group of compounds having a structure similar thereto.

Next, we will explain the prior art documents.

Document 1 describes in the abstract that there is a possibility that proliferative diabetic retinopathy (PDR) and macular edema (ME) can be prevented by glycemic control or amelioration of various abnormalities in the metabolism of sugar (AR inhibitor, antiglycation agent, PKC inhibitor). In fact, it is described that in regard to a PKC inhibitor, development has proceeded for diabetic retinopathy and macular edema and the effectiveness has been confirmed. However, in regard to an aldose reductase inhibitor (AR inhibitor), nothing is described about the effectiveness in macular edema. Moreover, it is described that although animal experiments show the effectiveness of an AR inhibitor in treating diabetic retinopathy, clinical investigation can find no effectiveness of an AR inhibitor (particularly, sorbinil). Thus, the reference shows a negative opinion about the AR inhibitor (page 242, 5 to 9 lines of the left column).

In addition, in documents 2 and 3, it is described that SNK-860 is effective for amelioration of retinal edema or diabetic simple retinopathy based on the results obtained from experimental animal model.

The following will describe what suggestion is given to a person with ordinary skill in the art when the person has read these documents. The person who has read document 1 is considered to recognize that a RKC inhibitor is effective for amelioration of diabetic retinopathy and macular edema but that it is difficult to show by clinical investigation that an AR

inhibitor is effective for amelioration of diabetic retinopathy and macular edema. A document should be determined regarding the described contents after having been read through but should not be determined on the basis of only partial description, i.e. the abstract. The person with ordinary skill in the art knows that clinical investigation in diabetic retinopathy has not shown effectiveness of many AR inhibitors even though the AR inhibitors are effective in animal experiment of diabetic retinopathy. Accordingly, the person is definitely supposed to reach the aforesaid conclusion.

Furthermore, when documents 1, 2 and 3 are combined, the person with ordinary skill in the art must receive the suggestion that in regard to SNK-860, it is difficult to show the effectiveness in clinical investigation of diabetic retinopathy or diabetic maculopathy although it is effective in an experimental animal model of diabetic retinopathy. In other words, the person with ordinary skill in the art will receive the similar suggestion regarding a group of compounds having similar structure, including SNK-860.

As obvious from the foregoing, it is considered that the prior art documents contain no description that motivates the invention of claim 1.

Here, Applicant shows an unpredictable advantageous effect of the invention of claim 1 by experimental data.

A certificate of experimental results which will be described later is a comparison between SNK-860 which is a most typical compound represented by the general formula [chemical formula 1] and epalrestat which is the only drug confirmed to

be effective in treating diabetic retinopathy by the clinical investigation, by using an experimental model of monkeys with diabetic maculopathy. As obvious from the data, epalrestat does not exert an effect when a dose thereof is increased within a range in which drug toxicity does not occur. However, SNK-860 suppresses macular edema even in lower doses. This is a distinguished difference and is said to be an unexpected advantageous effect.

Explaining the diabetic maculopathy again, tissues of the macula and the retina differ in morphology, and diabetic retinopathy and diabetic maculopathy are perceived as quite different diseases in textbooks and cannot be regarded as the same (following document 4). Furthermore, the effectiveness of SNK-860 in diabetic maculopathy has been confirmed by the clinical investigation described in the specification. Accordingly, SNK-860 is not necessarily effective in an experimental model.

Document 4: Hidetoshi Yamashita and Ryo Kawasaki ed., Diabetic Retinopathy: Best Advice By Medical Specialist, Tokyo, Shindann-to-Chryousha, 2003, pages 47-59.

(ii) The Invention of Claim 2 and Prior Art Documents

Claim 2 limits the compound to (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide which is used as an experimental example in the invention of a prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 1. Accordingly, it is considered that the prior art documents contain no description that motivates the invention of claim 2 and that the invention of claim 2 has an

unexpected advantageous effect, as described in regard to claim 1.

(iii) The Invention of Claim 3 and Prior Art Documents

Claim 3 limits an intended disease to macular edema or diabetic pigment epitheliopathy each of which is a specific symptom of diabetic maculopathy in the invention of a prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 1 or 2. The macular edema is especially an end-point in a pharmacological test. Accordingly, it is considered that the prior art documents contain no description that motivates the invention of claim 3 and that the invention of claim 3 has an unexpected advantageous effect, as described in regard to claim 1.

(iv) The Invention of Claim 4 and Prior Art Documents

Claim 4 limits the specific end-point in the diabetic maculopathy in the invention of a prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 1, to improvement of visual acuity or inhibition of deterioration of visual acuity in diabetic maculopathy. Accordingly, it is considered that the prior art documents contain no description that motivates the invention of claim 4 and that the invention of claim 4 has an unexpected advantageous effect, as described in regard to claim 1.

Additionally, it is considered to be an unexpected effect that the compound not only ameliorates edema but also improves visual acuity or prevents deterioration of visual acuity by clinical investigation.

(v) The Invention of Claim 5 and Prior Art Documents

Original claim 4 has been changed to independent claim 5 so that the invention is recited more clearly. Accordingly, claim 5 conforms to claim 4.

(vi) The invention of Claim 6 and Prior Art Documents

Claim 6 limits the compound to (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide which is used as an experimental example in the invention of a prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 5. Accordingly, claim 6 conforms to claim 5.

(vii) Conclusion

As obvious from the foregoing, the invention claimed in each of claims 1 to 6 is not described in the prior art documents, so it is not the invention under Patent Law Article 29 (1) (iii). Furthermore, the prior art documents contain no description that motivates the invention claimed in each of claims 1 to 6 and the invention has an unexpected advantageous effect. Accordingly, it is not the invention under Patent Law Article 29(2). Consequently, the invention claimed in each of claims 1 to 6 is patentable under Patent Law Article 29(1), main paragraph.

(3) A Certificate of Experimental Results

Next, a certificate of experimental results carried out regarding the present invention will be explained. The experiment is composed of three tests of A. pharmacological preliminary test 1 using crab-eating monkeys, B. pharmacological preliminary test 2 using crab-eating monkeys, and C. pharmacological test using crab-eating monkeys of experimental diabetes.

**A. Pharmacological preliminary test 1 using crab-eating monkeys -Epalrestat 400 mg/kg/day short-term repeated administration test-**

1. Purpose

The purpose of this test is to set a maximum effective dose of epalrestat used in macular edema evaluation study with streptozotocin (STZ) induced diabetic crab-eating monkey. The toxic dose level of epalrestat in the dog 3-month sub-acute toxicity test is estimated to be 500 mg/kg/day. A decreasing trend of the body weight is perceived at a 22nd day of administration by this dose[1)]. Based on the foregoing report, repeated administration of 400 mg/kg/day for 5 days was determined.

2. Experimental material and method

2.1. Test article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory Co., Ltd.) was employed as a test article.

2.2. Test method

2.2.1. Grouping

Four normal male crab-eating monkeys (Macaca fascicularis) from Nafovanny, Vietnam, ranging from 2 and 3 years old, were divided into two groups each of which was composed of two.

1) Control group (two monkeys)

2) Epalrestat 400 mg/kg/day administrated group (two monkeys)

2.2.2. Medication administration and blood drawing

A catheter was inserted from the buccal cavity through the

esophagus into the stomach so that an epalrestat suspension (prepared by 5% gum arabic solution) was administered. Administration was carried out three times a day (in the morning, daytime and at night) and repeated for five days. A 5% gum arabic solution was orally administered to the control group in a ratio of 5 ml/kg. The general condition and body weight were monitored every day in the administration period. Furthermore, blood was drawn from the saphena immediately before administration and five days after the administration using a disposable syringe barrel and needle without use of an anesthetic. Drawn blood was put into a Venoject II (Terumo Corporation) and left for 40 to 60 minutes at a room temperature. A biochemical examination using obtained blood serum was entrusted to the Corporation for Production and Research of Laboratory Primates.

3. Experimental results

3.1. General condition

No significant changes in the condition were found in each individual of the control group during the test. In the test article administered group, excretion of test article color-like urine was found from a first to fifth administration days regarding each individual. One of the monkeys had about 2 mL vomit of test article-like substance five days after administration, and another monkey had about 3 mL vomit of test article-like substance four and five days after administration.

3.2. Body Weight

TABLE 1 shows body weight changes. No significant changes in the body weight were found in each individual of the control

group during the test. In the test article administered group, one of the monkeys had weight loss of 0.2 kg five days after administration, and another monkey had weight loss of 0.3 kg five days after administration. The monkey which had the weight loss of 0.2 kg during five days died five days after cessation of the test article.

3.3. Biochemical examination of blood serum

TABLE 2 shows results of the examination. No changes were found in the control group before and after the administration. In the test article administered group, changes were found in each of BUN, GPT, LDH, CRE and T-BIL.

4. Summary

400 mg/kg/day epalrestat was considered to be a toxic dose based on aggravation of general condition, weight loss and variations in hepatic and kidney damage markers.

5. Reference

1) Katsumasa ISHIMURA, Hitoshi OGAWA, Koichi ISOWA, Hidetoshi KASHIMA and Shinji WATANABE, et al., Three-Month Subacute Toxicity Test and One-Month Recovery Test in Dogs by Oral Administration of ONO-2235, Modern Medical Care (Gendai-Iryou), 1986; 18 (Supplement III); p. 162-231. (attached as document 5)

TABLE 1 CHANGE IN BODY WEIGHT

| Group | Dose (mg/kg) | Animal | First day | Second day | Third day | Fourth day | Fifth day |
|---|---|---|---|---|---|---|---|
| Control | 0 | (1) | 2.4 | 2.3 | 2.3 | 2.3 | 2.3 |
| | | (2) | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Epalrestat | 400 | (1) | 2.5 | 2.5 | 2.5 | 2.5 | 2.3 |
| | | (2) | 2.5 | 2.4 | 2.4 | 2.3 | 2.2 |

TABLE 2 BIOCHMICAL EXAMINATION OF BLOOD SERUM

| Group | Dose (mg/kg) | Animal | BUN (mg/dL) | GOT (IU/L) | GPT (IU/L) | ALP (IU/L) | LDH (IU/L) |
|---|---|---|---|---|---|---|---|
| Control | 0 | (1) B | 18.8 | 26 | 29 | 1717 | 244 |
| | | (2) B | 23.8 | 21 | 16 | 2143 | 234 |
| Epalrestat | 400 | (1) B | 20.0 | 29 | 46 | 1934 | 270 |
| | | (2) B | 22.1 | 31 | 38 | 2546 | 233 |
| Control | 0 | (1) A | 20.8 | 27 | 35 | 2009 | 289 |
| | | (2) A | 27.8 | 25 | 21 | 2322 | 300 |
| Epalrestat | 400 | (1) A | 39.1 | 43 | 104 | 2138 | 778 |
| | | (2) A | 26.0 | 38 | 48 | 1914 | 287 |

where "B" designates the value before administration and "A" designates the value after administration for five days; and where BUN designates blood urea nitrogen, GOT glutamic-oxaloacetic transaminase, GPT glutamic-pyruvic transaminase, ALP alkaline phosphatase, LDH lactate dehydrogenase, CRE Creatinine and T-BIL total bilirubin.

TABLE 2 BIOCHMICAL EXAMINATION OF BLOOD SERUM -Continued-

| Group | Dose (mg/kg) | Animal | CRE (mg/dL) | T-BIL (mg/dL) |
|---|---|---|---|---|
| Control | 0 | (1) B | 0.5 | 0.2 |
| | | (2) B | 0.6 | 0.4 |
| Epalrestat | 400 | (1) B | 0.4 | 0.2 |
| | | (2) B | 0.5 | 0.2 |
| Control | 0 | (1) A | 0.5 | 0.2 |
| | | (2) A | 0.5 | 0.3 |

| | | | |
|---|---|---|---|
| Epalrestat 400 | (1) A | 1.5 | 0.4 |
| | (2) A | 1.1 | 0.7 |

**B. Pharmacological preliminary test 2 using crab-eating monkeys -Epalrestat 150 mg/kg/day short-term repeated administration test-**

1. Purpose

The purpose of this test is to set a maximum effective dose of epalrestat used in macular edema evaluation study with streptozotocin (STZ) induced diabetic crab-eating monkey. Since a toxic action was seen in the epalrestat 400 mg/kg/day short-term repeated administration test, inspection was carried out with the dose being reduced to 150 mg/kg/day.

2. Experimental material and method

2.1. Test article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory Co., Ltd.) was employed as a test article.

2.2. Test method

2.2.1. Grouping

Three normal male crab-eating monkeys (Macaca fascicularis) from Nafovanny, Vietnam, ranging from 2 and 3 years old, were used. Only one medication administration group was set in order that toxic action may be detected before and after administration.

1) Epalrestat 150 mg/kg/day administrated group (three monkeys)

2.2.2. Medication administration and blood drawing

A catheter was inserted from the buccal cavity through the esophagus into the stomach so that an epalrestat suspension (prepared by 5% gum arabic solution) was administered. Administration was carried out three times a day (in the morning, daytime and at night) and repeated for six days. The general condition and body weight were monitored every day in the administration period. Furthermore, blood was drawn from the saphena or femoral vein immediately before administration and six days after the administration using a disposable syringe barrel and needle without use of an anesthetic. Drawn blood was put into a Venoject II (Terumo Corporation) and left for 40 to 60 minutes at a room temperature. A biochemical examination using obtained blood serum was entrusted to the Corporation for Production and Research of Laboratory Primates.

3. Experimental results

3.1. General condition

In all the individuals, excretion of test article color-like urine was found from a first to sixth administration days.

3.2. Body Weight

TABLE 3 shows body weight changes. All the individuals had weight loss of 0.1 to 0.2 kg five or six days after administration.

3.3. Biochemical examination of blood serum

TABLE 4 shows results of the examination. By treatment with test article, changes were found in each of BUN, GPT, LDH and CRE.

4. Summary

Mild but temporal weight loss was seen and variations in hepatic and kidney damage markers were also seen, and accordingly, 150 mg/kg/day epalrestat was also considered to be a toxic dose.

TABLE 3 CHANGE IN BODY WEIGHT

| Group | Dose (mg/kg) | Animal | First day | Second day | Third day | Fourth day | Fifth day | Sixth day |
|---|---|---|---|---|---|---|---|---|
| Epalrestat | 150 | (1) | 2.3 | 2.3 | 2.2 | 2.2 | 2.1 | 2.1 |
| | | (2) | 2.3 | 2.4 | 2.3 | 2.2 | 2.1 | 2.1 |
| | | (3) | 2.4 | 2.4 | 2.4 | 2.4 | 2.3 | 2.3 |

TABLE 4 BIOCHMICAL EXAMINATION OF BLOOD SERUM

| Group | Dose (mg/kg) | Animal | BUN (mg/dL) | GOT (IU/L) | GPT (IU/L) | ALP (IU/L) | LDH (IU/L) |
|---|---|---|---|---|---|---|---|
| Epalrestat | 150 | (1) B | 19.4 | 34 | 17 | 2782 | 266 |
| | | (2) B | 19.4 | 36 | 30 | 1812 | 248 |
| | | (3) B | 16.5 | 44 | 19 | 2186 | 366 |
| | | (1) A | 46.6 | 57 | 139 | 2139 | 783 |
| | | (2) A | 46.9 | 35 | 58 | 1421 | 575 |
| | | (3) A | 15.7 | 27 | 17 | 2358 | 342 |

where "B" designates the value before administration and "A" designates the value after administration for six days; and where BUN designates blood urea nitrogen, GOT glutamic-oxaloacetic transaminase, GPT glutamic-pyruvic transaminase, ALP alkaline phosphatase, LDH lactate dehydrogenase, CRE Creatinine and T-BIL total bilirubin.

TABLE 4 BIOCHMICAL EXAMINATION OF BLOOD SERUM -Continued-

| Group | Dose (mg/kg) | Animal | CRE (mg/dL) | T-BIL (mg/dL) |
|---|---|---|---|---|
| Epalrestat | 150 | (1) B | 0.5 | 0.2 |
| | | (2) B | 0.5 | 0.2 |
| | | (3) B | 0.5 | 0.2 |
| | | (1) A | 4.9 | 0.2 |
| | | (2) A | 2.9 | 0.1 |
| | | (3) A | 0.9 | 0.2 |

**C. Pharmacological study using experimental diabetic crab-eating monkeys**

**-Action of SNK-860 and epalrestat against macular edema due to ischemic reperfusion-**

The effectiveness of aldose reductase inhibitor on macular edema due to ischemic reperfusion was compared regarding SNK-860 and epalrestat using streptozotocin (STZ) induced diabetic crab-eating monkeys (Macaca fascicularis).

2. Experimental material and method

2.1. Diabetes inducing substance and insulin

Diabetes mellitus was induced in monkeys by intravenously injecting streptozotocin (STZ: Lot No. 046K1206, Sigma) into their foreleg vein at the dose of 80 mg/kg. Insulin (NOVOLIN (registered trademark), NovoNordisk A/S) was administered subcutaneously twice a day (before feeding in the morning and in the evening). An applied dose of insulin was determined to be a slight amount necessary for subsistence (0.01 to 0.05

mL/body).

2.2. Test article

SNK-860 (Lot No. 901T-4) was employed as a test article. It is reported that SNK-860 suppresses 50% sorbitol accumulation at the dose of 2 mg/kg and 100% sorbitol accumulation at the dose of 16 mg/kg. Based on the report, the dose sufficiently suppressing sorbitol accumulation was set at 4 mg/kg/day and 8 mg/kg/day. Administration was carried out once a day (in the morning) for 14 days before increase in the intraocular pressure and for 7 days after increase in the intraocular pressure.

2.3. Control article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory Co., Ltd.) was employed as a control article. The dose was set at 25 mg/kg/day and 50 mg/kg/day based on the experiment results of preliminary test 1 and 2, and the report that 73% sorbitol accumulation was suppressed in the retina of a diabetic model at the dose of 50 mg/kg/day. Administration was carried out three times a day (in the morning, daytime and at night) for 14 days before increase in the intraocular pressure and for 7 days after increase in the intraocular pressure.

2.4. Test method

2.4.1. Grouping

STZ was administered to 20 male crab-eating monkeys (Macaca fascicularis) from Nafovanny, Vietnam, ranging from 2 and 3 years old, to induce diabetes mellitus. Surviving 16 monkeys were divided into four groups. The grouping was carried out three weeks after administration of STZ in view of glycated hemoglobin levels, body weight and results of general condition before

administration of medications (test article or control article). Groups were as follows:

1) Diabetic control group (4 monkeys);

2) Diabetic group of given 4 mg/kg SNK-860 (3 monkeys);

3) Diabetic group of given 8 mg/kg SNK-860 (3 monkeys);

4) Diabetic group of given 25 mg/kg epalrestat (3 monkeys); and

5) Diabetic group of given 50 mg/kg epalrestat (3 monkeys).

2.4.2. Preparation of retinal ischemia by increase of the intraocular pressure

Intraocular pressure was applied to both eyes of each monkey at a 14th day of administration by the following method:

A drip infusion set (Terufusion Drip Infusion Set manufactured by Terumo) was connected to a bottle containing an intraocular perfusion solution (Opeguard MA manufactured by Senju Pharmaceutical Co., Ltd.), and an extension tube to which a three-way stopcock had been attached was connected thereto. A needle was fitted to the end of the tube. The bottle was fixed to a stand so that a liquid level of the intraocular perfusion solution is 184 cm high relative to monkey's eyes. A mydriatic (Mydrin P manufactured by Santen Pharmaceutical Co., Ltd.) was dropped onto monkey's eye with sufficient mydriatic action. Thereafter, Ketalar (Sankyo Lifetech Co., Ltd.) was administered into muscle for anesthesia. Subsequently, a local anesthetic agent (Benoxyl eye drop 0.4%, Santen Pharmaceutical Co., Ltd.) was dropped and a lid retractor was then attached to prevent blinking. Ketalar was timely added. Thereafter, a needle was stuck into an anterior chamber of the monkey's eye and the three-way stopcock was operated so that pressure is applied in

the eye, whereby a retina ischemic condition was prepared. An ischemic time by application of intraocular pressure was set to 60 minutes. After application of the intraocular pressure, the needle was removed to relieve the intraocular pressure to allow reperfusion, and an antibacterial eye drop (tarivit eye ointment manufactured by Santen Pharmaceutical Co., Ltd.) was applied onto the eye. The thickness of macula was measured using an OCT scanner (Stratus OCT, Carl Zweiss Meditec AG) two days after application of intraocular pressure (16 days after medication administration) and four days after application of intraocular pressure (18 days after medication administration). Evaluation was carried out without consideration of eyeballs to which insufficient intraocular pressure was applied and in which macula was not observed by the OCT scanner.

2.4.3. Measurement of macula thickness

Macula cross-sectional imaging of the monkey under anesthesia was photographed using an OCT scanner on a fourteenth day from medication administration (immediately before application of intraocular pressure), a sixteenth day (two days after application of intraocular pressure) and eighteenth day (four days after application of intraocular pressure). Evaluation was carried out with respect to the minimum thickness of macula center.

2.4.4. Dissection

The monkeys were normally raised after application of intraocular pressure. Measurement of body weight and blood drawing were carried out 21 days after medication administration (seven days after application of intraocular pressure) and

thereafter, dissection was also carried out. Glycated hemoglobins were measured using drawn blood.

3. Test results

3.1. Effect on macular edema

TABLE 5 shows the results. A macular edema of diabetic monkey (an increase in the minimum thickness of macula center) was produced by application of intraocular pressure. The macular edema was seen during four days after application of intraocular pressure. Significant edema suppressing effect was admitted in the diabetic monkeys to which 4 or 8 mg/kg/day SNK-860 was administered. On the other hand, no significant edema suppressing effect was admitted in the diabetic monkeys to which 25 or 50 mg/kg/day epalrestat was administered.

3.2. Effect on body weight and glycated hemoglobin

TABLE 6 shows the results. No difference was seen among groups regarding body weight and glycated hemoglobin. Furthermore, the weight and hemoglobin were increased in all groups as compared with the time of grouping.

4. Summary

1) SNK-860 exhibited stronger suppression of macular edema in diabetes mellitus than epalrestat.

2) No effect was seen even when the dose of epalrestat was increased and accordingly, the effectiveness thereof against macular edema in diabetes mellitus was unclear. Addtionally, the set dose (25 and 50 mg/kg/day) was considered to have no controversial toxic effect.

3) The level of hemoglobin was rendered larger at the time of final administration than at the time of grouping, regarding all groups. Accordingly, the medicinal effect was considered to be brought by each medication but not by a blood glucose improving effect of insulin.

5. Reference

1) IG Obrosova, AG Minchenko, R Vasupuram, L. White, OI Abatan, AK Kumagai, RN Frank and MJ Stevens, Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871 (attached hereto as document 6).

2) N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura and N Sakamoto, Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats, Diabetologia 1985; 28; 176-180 (attached hereto as document 7).

TABLE 5 MINIMUM THICKNESS OF MACULAR CENTER AFTER APPLICATION OF INTRAOCULAR PRESSURE

| Group | Dose (mg/kg) | Number of eyes | Before application of intraocular pressure |
|---|---|---|---|
| Diabetic control | - | 7 | 135±3 |

| | | | |
|---|---|---|---|
| SNK-860 | 4 | 5 | 128±5 |
| | 8 | 6 | 131±5 |
| Epalrestat | 25 | 4 | 130±6 |
| | 50 | 6 | 128±4 |

TABLE 5 MINIMUM THICKNESS OF MACULAR CENTER

AFTER APPLICATION OF INTRAOCULAR PRESSURE -Continued-

| Group | Application of intraocular pressure | |
|---|---|---|
| | Two days after | Four days after |
| Diabetic control | 182±15 # | 152±6 # |
| SNK-860 | 139±10 * | 135±8 |
| | 140±7 * | 138±5 |
| Epalrestat | 164±22 | 152±9 |
| | 189±31 | 161±15 |

where average±standard error (μm), #p<0.05 versus before application of intraocular pressure, and *p<0.05 versus diabetic control.

TABLE 6 BODY WEIGHT AND GLYCATED HEMOGLOBIN

| Group | Dose (mg/kg) | Number of monkeys | Body Weight (kg) Grouping | Final |
|---|---|---|---|---|
| Diabetic control | - | 4 | 2.2±0.1 | 2.4±0.2 |
| SNK-860 | 4 | 3 | 2.3±0.4 | 2.4±0.4 |
| | 8 | 3 | 2.1±0.0 | 2.2±0.0 |
| Epalrestat | 25 | 3 | 2.2±0.2 | 2.3±0.1 |
| | 50 | 3 | 2.2±0.1 | 2.2±0.1 |

TABLE 6 BODY WEIGHT AND GLYCATED HEMOGLOBIN -Continued-

| Group | Glycated hemoglobin (%) | |
|---|---|---|
| | Grouping | Final |

| | | |
|---|---|---|
| Diabetic control | 7.7±0.8 | 8.2±0.7 |
| SNK-860 | 7.5±0.6 | 8.8±0.7 |
| | 8.0±0.2 | 9.2±0.2 |
| Epalrestat | 8.5±0.1 | 9.1±0.5 |
| | 7.9±1.8 | 8.8±1.8 |

where grouping designates "at the time of grouping" and final designates "at the time of final medication administration" and average±standard error

[List of filed articles]

[Name of article] Document 1: MA Speicher et al., Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging Drugs 2003; 8; 239-250.

[Name of article] Document 2: M Akita et al., Effects of an aldose reductase inhibitor, SNK-860, on the histopathological changes of retinal tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47: 299-304.

[Name of article] Document 3: JP-A-H07-242547 (attachment is eliminated)

[Name of article] Document 4: Hidetoshi Yamashita and Ryo Kawasaki ed., Diabetic Retinopathy: Best Advice By Medical Specialist, Tokyo, Shindann-to-Chiryousha, 2003, pages 47-59.

[Name of article] Document 5: Katsumasa ISHIMURA, Hitoshi OGAWA, Koichi ISOWA, Hidetoshi KASHIMA and Shinji WATANABE, et al., Three-Month Subacute Toxicity Test and One-Month Recovery Test in Dogs by Oral Administration of ONO-2235, Modern Medical Care (Gendai-Iryou)., 1986; 18 (Supplement III); p. 162-231.

[Name of article] Document 6: IG Obrosova, AG Minchenko, R

Vasupuram, L. White, OI Abatan, AK Kumagai, RN Frank and MJ Stevens, Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871.

[Name of article] Document 7: N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura and N Sakamoto, Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats, Diabetologia 1985; 28; 176-180.

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【氏名又は名称】　株式会社　三和化学研究所
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【識別番号】　１００１０８２８０
【弁理士】
【氏名又は名称】　小林　洋平
【電話番号】　０５９４－２７－５５１５
【早期審査に関する事情説明】
１．事情

欧州特許庁、米国特許庁、中国特許庁、韓国特許庁、カナダ特許庁、及びオーストラリア特許庁へ出願を行った。

欧州特許庁への出願の出願番号は０５７０４２３９．２である。米国特許庁への出願の出願番号は１０／５８７，３２０である。中国特許庁への出願の出願番号は２００５８００３６５９．１である。韓国特許庁への出願の出願番号は１０－２００６－７０１５８１２である。カナダ特許庁への出願の出願番号は２５５４６７９である。オーストラリア特許庁への出願の出願番号は２００５２０７９０６である。

２．先行技術の開示及び対比説明
（１）文献名

本願の原出願である国際特許出願（ＰＣＴ／ＪＰ２００５／１１８７）の国際予備審査によれば、本願発明に関連する文献は以下のとおりである。

文献１．MA Speicher et al.,Pharmacologic therapy for diabetic retinopathy, Expert

II(b)(i)

Opinion on Emerging Drugs 2003; 825269

文献２．M Akita et alEffects of aldose reductase inhibitor, SNK860, on the histopathological changes ofetinal tissues in atreptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47: 304299

文献３．特開平７－２４２５４７号公報

（２）対比説明

本願発明は、５月１４日付にて提出した手続補正書によって、補正されております。

(i)請求項１に記載の発明と先行技術文献

請求項１は、一般式[化１]で記載された化合物を有効成分とする糖尿病黄斑症の予防又は治療剤に係る発明です。この一般式で記載された化合物は、SNK-860 として知られる(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドを包含し、それに構造類似の化合物群です。

次に、先行技術文献について説明します。

文献１には、「増殖性糖尿病網膜症（PDR）及び黄斑浮腫（ME）は、血糖コントロールや各種糖代謝異常の改善（AR 阻害剤、抗グリケーション剤、PKC 阻害剤）により予防することができる可能性がある。」との記載がアブストラクトにあります。確かに、PKC 阻害剤については、糖尿病網膜症及び黄斑浮腫に対して開発が進んでいて、有効性が確認されていることが述べられています。しかし、アルドース還元酵素阻害剤（AR 阻害剤）については、黄斑浮腫に対する有効性について全く述べられていません。しかも、糖尿病網膜症においても、ＡＲ阻害剤は動物試験では有効性が見られるものの、臨床試験においては、有効性が見られない（特にソルビニル）との否定的な見解が示されています（ｐ242の左側5～9行目）。

また、文献２、３ですが、ここには、実験動物モデルでの結果に基づいて、SNK-860が網膜における浮腫又は糖尿病性単純網膜症の改善に有効である旨、記載されています。

次にこれらの文献を読んだ当業者がどのような示唆を受けるかについて説明します。

前記文献１を読んだ当業者は、PKC 阻害剤は糖尿病網膜症及び黄斑浮腫の改善に有効であるが、AR 阻害剤は、糖尿病網膜症又は黄斑浮腫の改善に、臨床試験で有効性を示すのは難しいとの認識をもつものと考えられます。文献は、あくまで全部を読んでそこに何が記載されているかを判断すべきであり、部分的な記載、即ち、アブストラクトのみの記載

で判断するものではありません。当業者は、多くのAR阻害剤が、糖尿病網膜症の動物実験では有効であったにもかかわらず、臨床試験で有効性が示されていないことを知っていますので、間違いなく、この結論に到達するはずです。

また、文献１と文献２，３を組み合わせた場合、当業者は、SNK-860についても、糖尿病性網膜症の実験動物モデルでは有効であるが、糖尿病性網膜症、糖尿病性黄斑症の臨床試験で有効性を示すのは難しいとの示唆を受けるはずです。即ち、SNK-860を含む構造類似の化合物群についても、同様の示唆を受けることになります。

以上より、先行技術文献には、本願請求項１に記載の発明の動機付けとなり得る記載はないものと考えられます。

ここで出願人は、更に、本願請求項１に記載の発明が予測できない有利な効果を有することを実験データでもって示すことにします。

後述の実験成績証明書は、一般式[化１]で記載された化合物の中で最も代表的な化合物であるSNK-860と、臨床試験で唯一、糖尿病性網膜症に対する有効性が確認されたエパルレスタットとを、糖尿病性黄斑症のサルの実験モデルで比較したものです。このデータからわかるように、エパルレスタットは、毒性が発現しない範囲で用量を上げても効果は見られませんが、SNK-860は、低用量で見事に黄斑浮腫を抑制しています。これは、全か無かの違いがある程の顕著な差であり、紛れもなく、予測できない有利な効果といえるものであります。

尚、糖尿病性黄斑症について再度説明させて頂きますと、組織的にも黄斑と網膜は異なる形態を有しており、糖尿病性黄斑症と糖尿病性網膜症は、教科書的にも、全く異なる疾患として捉えられており、同一視できるものではありません（下記文献４）。また、SNK-860の糖尿病性黄斑症に対する有効性は、明細書記載の臨床試験でも確認されており、実験モデルでしか効かないというものではありません。

文献４．山下英俊，川崎良編。糖尿病網膜症　専門医によるベストアドバイス。東京：診断と治療社；2003．p.4759.

(ii) 請求項２に記載の発明と先行技術文献

請求項２は、請求項１に係る糖尿病黄斑症の予防又は治療剤の発明において、化合物を実施例として使用されている(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミド（SNK-860）に限定したものです。ですから、先行技術文

献に、本願請求項２に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項１に関連して述べたとおりです。

(iii) 請求項３に記載の発明と先行技術文献

請求項３は、請求項１又は２に係る糖尿病黄斑症の予防又は治療剤において、糖尿病黄斑症の具体的な症状である黄斑浮腫又は糖尿病色素上皮症に使用対象を限定したものです。黄斑浮腫は特に、薬理試験における評価項目ともなっているものです。ですから、先行技術文献に、本願請求項３に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項１に関連して述べたとおりです。

(iv) 請求項４に記載の発明と先行技術文献

請求項４は、請求項１に係る糖尿病黄斑症の予防又は治療剤において、糖尿病黄斑症における具体的な評価項目を限定、即ち、視力の改善又は低下防止剤として使用されるという限定を加えたものです。ですから、先行技術文献に、本願請求項３に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項１に関連して述べたとおりです。

尚、単に浮腫改善をするだけでなく、より直接的に視力の改善又は低下防止効果を臨床試験で証明したところは、予測できない効果と言えるものと考えます。

(v) 請求項５に記載の発明と先行技術文献

請求項５は、文言をすっきりさせるために、請求項４を独立クレーム化したものです。ですから、請求項４に準じます。

(vi) 請求項６に記載の発明と先行技術文献

請求項６は、請求項５の発明において、化合物を実施例として使用されている(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミド（SNK-860）に限定したものです。ですから、請求項５に準じます。

(vii)結論

上記の通りであり、本願の請求項 1～6 に係る各発明は、先行技術文献に記載されていませんので、特許法第 29 条第 1 項第 3 号に該当する発明ではありません。また更に、本願の請求項 1～6 に係る各発明は、先行技術文献には動機付けとなり得る記載はなく、しかも、予測できない有利な効果を奏しますので、特許法第 29 条第 2 項に該当する発明でもありません。従って、特許法第 29 条第 1 項柱書きの規定により特許を受けることがで

きる発明に該当するものです。

（3）実験成績証明書

次に、本発明に関して行った実験成績証明を説明する。実験は、A．カニクイザルを用いた薬効薬理予備試験１、B．カニクイザルを用いた薬効薬理予備試験２、及びC．実験的糖尿病カニクイザルを用いた薬効薬理試験の三種類から構成されている。

A．カニクイザルを用いた薬効薬理予備試験１

ーエパルレスタット 400 mg/kg/day 短期連投試験ー

１．目的

streptozotocin(STZ)誘発糖尿病カニクイザル黄斑浮腫評価試験に用いるエパルレスタットの最大有効用量を設定する。尚、イヌ３ヶ月亜急性毒性試験におけるエパルレスタットの確実中毒量は500 mg/kg/dayと推察され，この用量では投与22日目より体重の減少傾向が認められている[1)]。以上の報告から今回，400 mg/kg/dayの５日間投与とした。

２．実験材料及び実験方法

2.1. 被験物質

エパルレスタット（Lot NoEPA-06510，三洋化学研究所）を被験物質とした。

2.2. 実験方法

2.2.1. 群分け

2～3 歳の健常雄性カニクイザル（ベトナム NAFOVANNY 産）4 頭を 2 頭ずつ以下の 2 群に分けた。

1) 対照群（2 頭）

2) エパルレスタット 400 mg/kg/da投与群（2 頭）

2.2.2. 薬物投与及び採血

カテーテルを口腔より食道を経て胃内に挿入し，エパルレスタット投与液（5%アラビアゴム溶液で調製）を投与した。投与期間は5日間とし，1日3回に分け投与した（朝，昼，夜）。尚，対照群には5%アラビアゴム溶液を5 mL/kgの割合で経口投与した。一般状態の観察及び体重測定は投与期間中毎日行った。また血液は無麻酔で，ディスポーザブル注射筒及び針を用いて，投与直前及び投与5日後に伏在静脈から採取した。得られた血液をヘ

ノジェクトII（テルモ）に入れ 40～60 分室温で放置した。得られた血清を用いての生化学検査は予防衛生協会に委託して行った。

3．実験結果

3.1. 一般状態

対照群では，試験期間中，各個体において，特記すべき一般状態の変化はみられなかった。被験物質投与群では，各個体とも投与 1 日後から 5 日後まで「被験物質様色調の尿排泄」がみられた。1 頭は投与 5 日後に「被験物質様物質の嘔吐,約 2 mL を，別の 1 頭は投与 4 日後及び 5 日後に「被験物質様物質の嘔吐,約 3 mL を示した。

3.2. 体重

体重の推移を表 1 に示す。対照群では，試験期間中，各個体において，特記すべき体重の変化は認められなかった。被験物質投与群では，1 頭が投与 5 日後に 0.2kg の減少を，別の 1 頭が投与 5 日後に 0.3kg の減少を示した。尚，5 日間で 0.2kg 体重が減少した個体は休薬 5 日後に死亡した。

3.3. 血清生化学的検査

結果を表 2 に示す。対照群では，投与前後での変動は認められなかった。被験物質投与群では，BUN, GPT, LDH, CRE, T-BIL で変化が認められた。

4．まとめ

一般状態の悪化，体重減少及び肝障害腎障害マーカーの変動から，エパルレスタット 400 mg/kg/day は毒性用量と考えられた。

5．参考文献

1) 石村勝正，小川 仁，磯和弘一，鹿島秀敏，渡辺進二他. ONO-2235 の経口投与におけるイヌでの 3 ヵ月亜急性毒性試験および 1 ヵ月回復試験. 現代医療 1986; 18（増 III）: 162-231.（文献 5 として添付）

【表１】

表１ 体重の推移

| 群 | 用量 (mg/kg) | 動物 | 1日目 | 2日目 | 3日目 | 4日目 | 5日目 |
|---|---|---|---|---|---|---|---|
| 対照 | 0 | ① | 2.4 | 2.3 | 2.3 | 2.3 | 2.3 |
| | | ② | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| エバルレスタット | 600 | ① | 2.5 | 2.5 | 2.5 | 2.5 | 2.3 |
| | | ② | 2.5 | 2.4 | 2.4 | 2.3 | 2.2 |

(kg)

【表２】

表２ 血清学的検査

| 群 | 用量 (mg/kg) | 動物 | BUN (mg/dL) | GOT (IU/L) | GPT (IU/L) | ALP (IU/L) | LDH (IU/L) | CRE mg/dL | T-BIL (mg/dL) |
|---|---|---|---|---|---|---|---|---|---|
| 対照 | 0 | ①前 | 18.8 | 26 | 29 | 1717 | 241 | 0.5 | 0.2 |
| | | ②前 | 23.8 | 21 | 16 | 2143 | 234 | 0.6 | 0.4 |
| エバルレスタット | 400 | ①前 | 20.0 | 29 | 46 | 1934 | 270 | 0.4 | 0.2 |
| | | ②前 | 22.1 | 31 | 38 | 2546 | 231 | 0.5 | 0.2 |
| 対照 | 0 | ①後 | 20.8 | 27 | 35 | 2009 | 289 | 0.5 | 0.2 |
| | | ②後 | 27.8 | 25 | 21 | 2322 | 300 | 0.5 | 0.3 |
| エバルレスタット | 400 | ①後 | 39.1 | 43 | 104 | 3136 | 776 | 1.5 | 0.4 |
| | | ②後 | 36.0 | 38 | 48 | 1914 | 287 | 1.5 | 0.7 |

"前"は投与前の値を示し、"後"は5日目の投与後の値を示す。
BUN:尿素窒素, GOT:グルタミン酸オキサロ酢酸トランスアミナーゼ
GPT:グルタミン酸ピルビン酸トランスアミナーゼ, ALP:アルカリホスファターゼ
LDH:乳酸脱水素酵素, CRE:クレアチニン, T-BIL:総ビリルビン

【表1】

表1 体重の推移

| 群 | 用量 (mg/kg) | 動物 | 1日目 | 2日目 | 3日目 | 4日目 | 5日目 |
|---|---|---|---|---|---|---|---|
| 対照 | 0 | ① | 2.4 | 2.3 | 2.3 | 2.3 | 2.3 |
| | | ② | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| エバルレスタット | 600 | ① | 2.5 | 2.5 | 2.5 | 2.5 | 2.3 |
| | | ② | 2.5 | 2.4 | 2.4 | 2.3 | 2.2 |

(kg)

【表2】

表2 血清学的検査

| 群 | 用量 (mg/kg) | 動物 | BUN (mg/dL) | GOT (IU/L) | GPT (IU/L) | ALP (IU/L) | LDH (IU/L) | CRE (mg/dL) | T-BIL (mg/dL) |
|---|---|---|---|---|---|---|---|---|---|
| 対照 | 0 | ①前 | 18.8 | 26 | 29 | 1717 | 344 | 0.5 | 0.2 |
| | | ②前 | 23.8 | 21 | 16 | 2143 | 234 | 0.6 | 0.4 |
| エバルレスタット | 400 | ①前 | 20.0 | 29 | 46 | 1934 | 270 | 0.4 | 0.2 |
| | | ②前 | 22.1 | 31 | 38 | 2546 | 233 | 0.5 | 0.2 |
| 対照 | 0 | ①後 | 20.8 | 27 | 35 | 2009 | 289 | 0.5 | 0.2 |
| | | ②後 | 27.8 | 25 | 21 | 2322 | 300 | 0.5 | 0.3 |
| エバルレスタット | 400 | ①後 | 39.1 | 43 | 104 | 3158 | 775 | 1.5 | 0.4 |
| | | ②後 | 36.0 | 38 | 48 | 1914 | 287 | 1.5 | 0.7 |

"前"は投与前の値を示し、"後"は5日目の投与後の値を示す。
BUN:尿素窒素, GOT:グルタミン酸オキサロ酢酸トランスアミナーゼ
GPT:グルタミン酸ピルビン酸トランスアミナーゼ, ALP:アルカリホスファターゼ
LDH:乳酸脱水素酵素, CRE:クレアチニン, T-BIL:総ビリルビン

B．カニクイザルを用いた薬効薬理予備試験２

ーエパルレスタット 150 mg/kg/day 短期連投試験ー

１．目的

streptozotocin(STZ)誘発糖尿病カニクイザル黄斑浮腫評価試験に用いるエパルレスタットの最大有効用量を設定する。尚、エパルレスタット 400 mg/kg/da短期連投試験において毒性作用がみられた為，用量を 150 mg/kg/dayに下げて検討した。

２．実験材料及び実験方法

2.1. 被験物質

エパルレスタット（Lot NoEPA-06510，三洋化学研究所）を被験物質とした。

2.2. 実験方法

2.2.1. 群分け

2～3 歳の健常雄性カニクイザル（ベトナム NAFOVANNY 産）3 頭を使用した。薬物投与前後で影響を検討する為，今回薬物投与群 1 群のみとした。

1) エパルレスタット 150 mg/kg/da投与群（3 頭）

2.2.2. 薬物投与及び採血

カテーテルを口腔より食道を経て胃内に挿入し，エパルレスタット投与液（5%アラビアゴム溶液で調製）を投与した。投与期間は 6 日間とし，1 日 3 回に分け投与した（朝，昼，夜）。一般状態の観察及び体重の測定は投与期間中毎日行った。また血液は無麻酔で，ディスポーザブル注射筒及び針を用いて，投与直前及び投与 5 日後に伏在静脈もしくは大腿静脈から採取した。得られた血液をベノジェクトⅡ（テルモ）に入れ 40～60 分室温で放置した。得られた血清を用いての生化学検査は予防衛生協会に委託して行った。

３．実験結果

3.1. 一般状態

全ての個体において，投与 1 日後から 6 日後まで「被験物質様色調の尿排泄」がみられた。

3.2. 体重

体重の推移を表３に示す。全ての個体において，投与 5 日後から 6 日後に 0.1～0.2kg

の減少がみられた。

3.3. 血清生化学的検査

結果を表４に示す。被験物質投与によって，BUN，GPT，LD及びCREで変化が認められた。

４．まとめ

軽度ではあるが経時的な体重減少がみられ，また肝障害腎障害マーカーの変動もみられた事から，150 mg/kg/dayの用量も毒性用量と考えられた。

【表３】

表３ 体重の推移

| 群 | 用量 (mg/kg) | 動物 | 1日目 | 2日目 | 3日目 | 4日目 | 5日目 | 6日目 |
|---|---|---|---|---|---|---|---|---|
| エパルレスタット | 150 | ① | 2.3 | 2.3 | 2.2 | 2.2 | 2.1 | 2.1 |
| | | ② | 2.3 | 2.4 | 2.3 | 2.2 | 2.1 | 2.1 |
| | | ③ | 2.4 | 2.4 | 2.4 | 2.4 | 2.3 | 2.3 |

(kg)

【表４】

表４ 血清学的検査

| 群 | 用量 (mg/kg) | 動物 | BUN (mg/dL) | GOT (IU/L) | GPT (IU/L) | ALP (IU/L) | LDH (IU/L) | CRE (mg/dL) | T-BIL (mg/dL) |
|---|---|---|---|---|---|---|---|---|---|
| エパルレスタット | 150 | ①前 | 19.4 | 34 | 17 | 2782 | 366 | 0.5 | 0.2 |
| | | ②前 | 19.4 | 36 | 30 | 1812 | 348 | 0.5 | 0.3 |
| | | ③前 | 16.5 | 44 | 19 | 2186 | 356 | 0.5 | 0.2 |
| | | ①後 | 46.6 | 57 | 139 | 2139 | 783 | 4.9 | 0.2 |
| | | ②後 | 46.9 | 35 | 58 | 1421 | 575 | 2.9 | 0.1 |
| | | ③後 | 35.7 | 27 | 17 | 2358 | 342 | 0.9 | 0.2 |

"前"は投与前の値を示し，"後"は6日間の投与後の値を示す。
BUN：尿素窒素，GOT：グルタミン酸オキサロ酢酸トランスアミナーゼ
GPT：グルタミン酸ピルビン酸トランスアミナーゼ，ALP：アルカリホスファターゼ
LDH：乳酸脱水素酵素，CRE：クレアチニン，T-BIL：総ビリルビン

C．実験的糖尿病カニクイザルを用いた薬効薬理試験

－SNK-860及びエパルレスタットの虚血再灌流による黄斑浮腫に対する作用－

1．目的

streptozotocin(STZ)誘発糖尿病カニクイザルの網膜に虚血再灌流処理を施して，黄斑に浮腫を発現させた糖尿病黄斑症モデルを用いて，アルドース還元酵素阻害剤の有効性をSNK-860及びエパルレスタットについて比較検討した。

2．実験材料及び実験方法

2.1. 糖尿病惹起物質及びインスリン

糖尿病はstreptozotocin (STZ: Lot No. 046K1206, Sigma)を前肢橈側皮静脈より80 mg/kgの用量で投与して惹起した。STZ投与翌日から剖検前日まで，血糖値が250 mg/dL以上を示した場合，インスリン(ノボリン（登録商標）30R注100，ノボノルディスクファーマ)を皮下注射した（原則1日2回（朝：給餌直前，夕)。尚，インスリンの投与量は生存させる為に必要な少量（0.01～0.05 mL/body）とした。

2.2. 被験物質

SNK-860(Lot No. 901T-4）を被験物質とした。SNK-860は糖尿病モデルでの網膜中ソルビトール蓄積を2 mg/kgで50%抑制し，16 mg/kgで100%抑制することが報告されている[1]。この報告からソルビトール蓄積を充分抑制する用量として，4 mg/kg/day及び8 mg/kg/dayを設定した。尚，投与は1日1回（朝）とし，眼圧負荷前14日間及び眼圧負荷後7日間行った。

2.3. 対照物質

エパルレスタット（Lot No. EPA-06510，三洋化学研究所）を対照物質とした。用量は予備試験1及び2の成績及び50 mg/kgの用量で糖尿病モデルでの網膜中ソルビトール蓄積を73%抑制するという報告[2]を基に，25 mg/kg/day及び50 mg/kg/dayを設定した。尚，投与は臨床用法に準じ1日量を3回に分けて，朝，昼及び夜に行い，眼圧負荷前14日間及び眼圧負荷後7日間行った。

2.4. 実験方法

2.4.1. 群分け

2～3歳の雄性カニクイザル(ベトナムNAFOVANNY産) 20頭にSTZを投与して糖尿病を惹

起した。糖尿病惹起後，生存した16頭を群分けした。群分けは薬物（被験物質又は対照物質）投与前のグリコヘモグロビン値，体重値及び一般状態の結果を考慮してSTZ投与3週後に行った。群分けは以下の通りとした。

1) 糖尿病対照群（4頭）

2) SNK-860 4 mg/kg投与糖尿病群（3頭）

3) SNK-860 8 mg/kg投与糖尿病群（3頭）

4) エパルレスタット 25 mg/kg投与糖尿病群（3頭）

5) エパルレスタット 50 mg/kg投与糖尿病群（3頭）

2.4.2. 眼圧負荷による網膜虚血の作製

薬物投与開始14日目に各サルの両眼に眼圧負荷を行った。眼圧負荷の方法は以下の通りである。

眼内灌流液（オペガードMA，千寿製薬）の入ったボトルに輸液セット（テルフュージョン輸液セット）を接続し，それに三方活栓を付けた延長チューブ（エックステンションチューブ）を接続した。チューブの先端には注射針を装着した。眼内灌流液の入ったボトルの水面がサルの目の位置から184 cmの高さになるようにボトルをスタンドに固定した。サル眼に散瞳薬（ミドリンP，参天製薬）を滴下し充分に散瞳した後，ケタラール（三共ライフテック）を筋肉内に投与して麻酔した。続いて局所麻酔薬（ベノキシール点眼液0.4%，参天製薬）を点眼し，開瞼器をつけて瞬きをしないようにした。ケタラールは適時追加した。その後サルの前眼房に注射針を刺入し，三方活栓を操作して眼内に圧力を負荷し網膜虚血状態を作製した。眼圧負荷による虚血時間は60分間とした。眼圧負荷後，注射針を抜いて眼圧負荷を解除するとともに再灌流を行い，抗菌剤（タリビット眼軟膏，参天製薬）を眼に充分塗布した。眼圧負荷2日（薬物投与16日）後及び4日（薬物投与18日）後に黄斑部の厚さをOCTスキャナー（Stratus OCT：カールツァイスメディテック）を用いて測定した。眼圧負荷が充分でなかった眼球及びOCTスキャナーで黄斑観察ができなかった眼球は評価から外した。

2.4.3. 黄斑部の厚さの測定

薬物投与開始14日目（眼圧負荷直前），16日目（眼圧負荷2日後），18日目（眼圧負荷4日後）に，麻酔下でOCTスキャナーを用いてサルの黄斑断層像を撮影した。評価は黄斑中心の最小厚について行った。

2.4.4. 解剖

サルは眼圧負荷後，通常飼育を行った。薬物投与開始21日後（眼圧負荷7日後）に体重測定及び採血を行った後，解剖した。採血した血液を用いて，グリコヘモグロビン測定を行った。

3．実験結果

3.1. 黄斑浮腫に対する作用

結果を表5に示す。眼圧負荷により糖尿病サルの黄斑浮腫（黄斑中心の最小厚の肥厚）が確認され，この浮腫は眼圧負荷4日後までみられた。SNK-860 4 mg/kg/day 又は 8 mg/kg/day を投与した糖尿病サルでは有意な浮腫抑制作用が認められた。一方，エパルレスタット25 mg/kg/day 又は50 mg/kg/day を投与した糖尿病サルでは有意な浮腫抑制作用は認められなかった。

3.2. 体重及びグリコヘモグロビンに対する作用

結果を表6に示す。体重及びグリコヘモグロビンは群間に差がみられなかった。また、全群，群分け時より体重が増加し，ヘモグロビン値も増加した。

4．まとめ

1) SNK-860はエパルレスタットに比して，糖尿病時の黄斑浮腫発現に対して強い抑制作用を示した。

2) エパルレスタットは，用量を上げても効果が見られず、糖尿病時の黄斑浮腫に対する有効性は明らかではなかった。尚，今回の設定用量（25 mg/kg/day，50 mg/kg/day）では，問題となる毒性作用は無いと考えられた。

3) 全群，群分け時より最終投与時でグリコヘモグロビン値が増加していた。このことから，今回の薬効は各薬物によるものであり，インスリンの血糖改善作用によるものでないと考えられた。

5．参考文献

1) IG Obrosova, AG Minchenko, R Vasupuram, L White, OI Abatan, AK Kumagai, RN Frank, MJ Stevens. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress

and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871. (文献６として添付)

2) N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura, N Sakamoto. Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats. Diabetologia 1985; 28: 176-180. (文献７として添付)

【表５】

表5 眼圧負荷後の黄斑中心の最小厚

| 群 | 用量 (mg/kg) | 眼数 | 眼圧負荷前 | 眼圧負荷 2日後 | 眼圧負荷 4日後 |
|---|---|---|---|---|---|
| 糖尿病対照 | − | 7 | 135±3 | 182±15 #,* | 152±6 # |
| SNK-860 | 4 | 5 | 128±5 | 139±10 | 135±8 |
| | 8 | 6 | 131±5 | 140±7 | 136±5 |
| エパルレスタット | 25 | 4 | 130±6 | 164±22 | 152±9 |
| | 50 | 6 | 128±4 | 159±13 | 161±15 |

平均値±標準誤差(μm)。 #p<0.05 対眼圧負荷前、*p<0.05 対糖尿病対照

【表６】

表6 体重及びグリコヘモグロビン

| 群 | 用量 (mg/kg) | 匹数 | 体重(kg) 群分け | 体重(kg) 最終 | グリコヘモグロビン(%) 群分け | グリコヘモグロビン(%) 最終 |
|---|---|---|---|---|---|---|
| 糖尿病対照 | − | 4 | 2.2±0.1 | 2.4±0.2 | 7.7±0.8 | 8.2±0.7 |
| SNK-860 | 4 | 3 | 2.3±0.4 | 2.4±0.4 | 7.5±0.6 | 8.3±0.7 |
| | 8 | 3 | 2.1±0.0 | 2.2±0.0 | 8.0±0.2 | 9.2±0.2 |
| エパルレスタット | 25 | 3 | 2.2±0.2 | 2.3±0.1 | 8.3±0.1 | 9.1±0.5 |
| | 50 | 3 | 2.2±0.0 | 2.3±0.1 | 7.9±1.0 | 8.8±1.8 |

群分け:個分け時 最終:最終観察日
平均±標準偏差

【提出物件の目録】

【物件名】 文献1. MA Speicher et al.,Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging Drugs 2003; 8:229-239 1

【物件名】 文献2. M Akita et al., Effects of an aldose reductase inhibitor, SNK-860, on the histopathological changes of retinal tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47:299-304. 1

【物件名】 文献3. 特開平7－242547号公報（添付を省略する）

【物件名】 文献4. 山下英俊, 川崎良編。糖尿病網膜症 専門医によるベストアドバイス。東京：診断と治療社；2003. p.47-59. 1

【物件名】 文献5. 石村勝正, 小川 仁, 磯和弘一, 鹿島秀敏, 渡辺進二他. ONO-2235の経口投与におけるイヌでの3ヵ月亜急性毒性試験および1ヵ月回復試験. 現代医療 1986; 18（増III）：162-231. 1

【物件名】 文献6. IG Obrosova, AG Minchenko, R Vasupuram, L White, OI Abatan, AK Kumagai, RN Frank, MJ Stevens. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871. 1

【物件名】 文献7. N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura, N Sakamoto. Effects of sucrose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats. Diabetologia 1992; 35: 176-180. 1

(English translation)
Reference: Dispatch No. 348188 Dispatch Date:18/07/2007

**NOTIFICATION OF REASONS FOR REFUSAL**

Patent Application No. Patent Application No. 2005-517502
Drafting Date 10th July 2007
Examiner of JPO Hirofumi TOUMA, Serial No. 3543-4C00
Representative of Applicant Yohei KOBAYASHI
Applied Provision Patent Law Section 36

This application should be refused for the reason mentioned below. If the applicant has any argument against the reason, such argument should be submitted within 60 days from the date on which this notification was dispatched.

Reason

Reason 1:
Claims 1 and 3 to 5
Notes:
The definition of each substituent group in claims 1 and 5 contains the description of an optionally substituted C1 to C6 alkyl group. But by what range of functional group C1-6 alkyl group may be replaced is not definitely specified.

<Claims for which a reason for refusal has not been found>
No reason for refusal has been found regarding the invention claimed in each of claims 2 and 6. A new reason for refusal will be notified when having been found.

(*) Please note that no new matter must be added to when you file amendment. Furthermore, on this occasion, it is recommended that the part of the specification or drawings that supports amendment is clearly indicated in remarks.

---

Record of Result of Prior Art Document Search

Searched Fields IPC C07D491/107,

A61K 31/33 to 33/44,
A61P 27/02,

Data Base Name CAPLUS (STN),
CAOLD (STN),
REGISTRY (STN),
MEDLINE (STN),
BIOSIS (STN),
EMBASE (STN),
WPIDS (STN)

Prior art documents
1. SPEICHER M.A. et al., Expert Opinion on Emerging Drugs 2003, Vol. 8/No. 1, p. 239-250.;
2. Akita, M et al., Acta. Med. Okayama, 1993, Vol. 47/No. 5, p.299-304;
3. JP-A-H07-242547;
4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, 2003, Vol.4/No.10, p1233-1239; and
5. FERRIS, III, F.L., Survey of Ophthalmology, 2002, vol47/Suppl. 2, p. S237.

This record is not a component(s) of the reason(s) for refusal.

Please contact the following when you have any inquiry about the contents of this notification of reason for refusal or when you would like to conduct a personal interview:

Hirofumi TOUMA, 3rd Examination Department, Patent Office
Telephone 03-3581-1101 (Extension 3490)
Facsimile 03-3581-1342

A61K 31/33 to 33/44,
A61P 27/02,

Data Base Name CAPLUS (STN),
CAOLD (STN),
REGISTRY (STN),
MEDLINE (STN),
BIOSIS (STN),
EMBASE (STN),
WPIDS (STN)

Prior art documents
1. SPEICHER M.A. et al., Expert Opinion on Emerging Drugs 2003, Vol. 8/No. 1, p. 239-250.;
2. Akita, M et al., Acta. Med. Okayama, 1993, Vol. 47/No. 5, p.299-304;
3. JP-A-H07-242547;
4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, 2003, Vol.4/No.10, p1233-1239; and
5. FERRIS, III, F.L., Survey of Ophthalmology, 2002, vol47/Suppl. 2, p. S237.

This record is not a component(s) of the reason(s) for refusal.

Please contact the following when you have any inquiry about the contents of this notification of reason for refusal or when you would like to conduct a personal interview:

Hirofumi TOUMA, 3rd Examination Department, Patent Office
Telephone 03-3581-1101 (Extension 3490)
Facsimile 03-3581-1342

整理番号: 発送番号:348188 発送日:平成19年 7月18日 1

# 拒絶理由通知書

| | |
|---|---|
| 特許出願の番号 | 特願２００５－５１７５０２ |
| 起案日 | 平成１９年 ７月１０日 |
| 特許庁審査官 | 當麻 博文 ３５４３ ４Ｃ００ |
| 特許出願人代理人 | 小林 洋平 様 |
| 適用条文 | 第３６条 |

この出願は、次の理由によって拒絶をすべきものである。これについて意見があれば、この通知書の発送の日から６０日以内に意見書を提出して下さい。

理 由

１．この出願は、特許請求の範囲の記載が下記の点で、特許法第３６条第６項第２号に規定する要件を満たしていない。

記

・理由 1
・請求項 1，３～５
・備考
請求項１，５における各置換基の定義において、「置換されていてもよいＣ１－６アルキル基」なる記載があるが、具体的にどのような範囲の官能基で置換されていてもよいのか、その範囲が明確に規定されているとはいえない。

<拒絶の理由を発見しない請求項>
請求項２，６に係る発明については、現時点では、拒絶の理由を発見しない。拒絶の理由が新たに発見された場合には拒絶の理由が通知される。

（＊）補正をするときは、新規事項の追加にならないよう留意されたい。また、その際、補正の根拠となる明細書又は図面中の該当記載箇所について意見書中で明示されることが望ましい。

---

先行技術文献調査結果の記録

・調査した分野 ＩＰＣ Ｃ０７Ｄ４９１／１０７，
Ａ６１Ｋ ３１／３３～３３／４４，
Ａ６１Ｐ ２７／０２，

I(a)(i)

整理番号: 発送番号:348188 発送日:平成19年 7月18日 2/E

DB名 CAPLUS (STN),
CAOLD (STN),
REGISTRY (STN),
MEDLINE (STN),
BIOSIS (STN),
EMBASE (STN),
WPIDS (STN)

・先行技術文献

1. SPEICHER, M.A. et al., Expert Opinion on Emerging Drugs, ２００３年, Vol.8/No.1, p.239-250
2. AKITA, M. et al., Acta. Med. Okayama, １９９３年, Vol.47/No.5, p.299-304
3. 特開平７－２４２５４７号公報
4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, ２００３年, Vol.4/No.10, p.1233-1239
5. FERRIS, III, F.L., Survey of Ophthalmology, ２００２年, Vol.47/Suppl.2, p.S237

この先行技術文献調査結果の記録は、拒絶理由を構成するものではない。

この拒絶理由通知の内容に関するお問い合わせ、または面接のご希望がございましたら下記までご連絡下さい。

特許審査第三部 医療 苫麻（とうま） 博文
ＴＥＬ. ０３（３５８１）１１０１ 内線３４９０
ＦＡＸ. ０３（３５８１）１３４２

[Document Name] AMENDMENT

[Reference] P06023SKK

[Filing Date] 3rd August 2007

[Address] To the Commissioner, Patent Office

[Case Identification]

[Application Number] Patent Application No. 2005-517502

[Amender]

[Identification Number] 000144577

[Name] SANWA KAGAKU KENKYUSHO CO., LTD.

[Agent]

[Identification Number] 100108280

[Patent Attorney]

[Name] KOBAYASHI Youhei

[Telephone] 0594-27-5515

[Amendment 1]

[Amended Document] CLAIMS

[Amended Item] Whole Document

[Amending Method] Modification

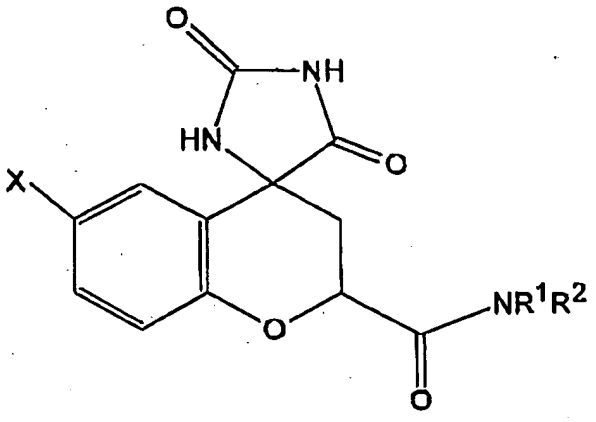
[Amendment Contents]

[Document Name] CLAIMS

[Claim 1]

A prophylactic or therapeutic agent for diabetic maculopathy, comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula 1]




(wherein X represents a halogen or a hydrogen atom, $R^1$ and $R^2$ concurrently or differently represent a hydrogen atom or a C1 to C6 alkyl group, or $R^1$ and $R^2$ together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 2] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

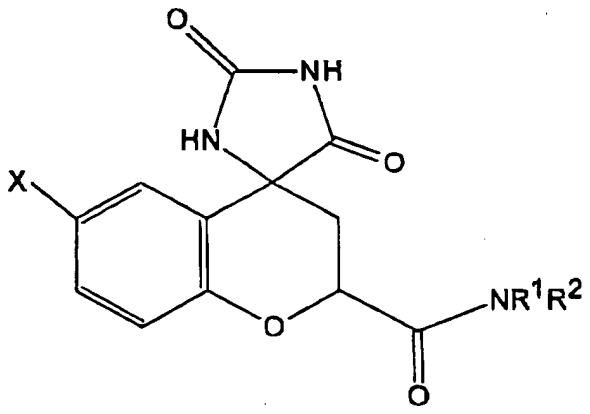
[Claim 3] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use in macular edema or in retinal pigment epitheliopathy in diabetic maculopathy.

[Claim 4] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use as an agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy.

[Claim 5] An agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy,

comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula]

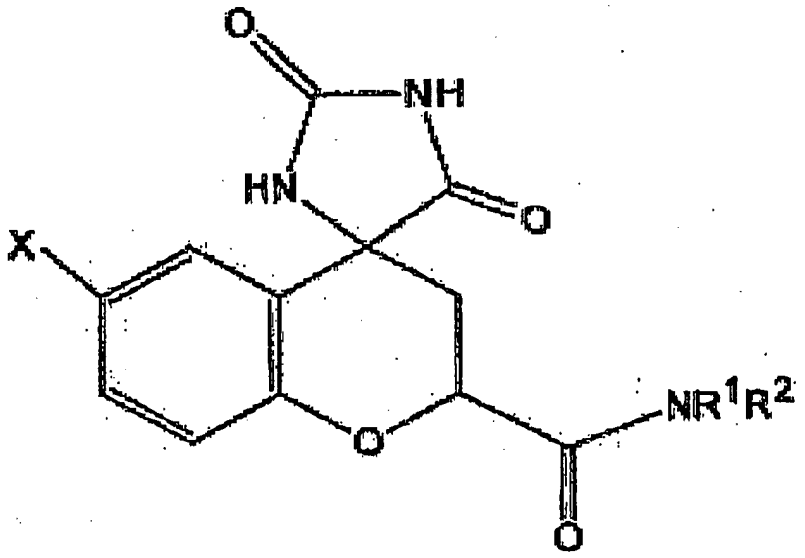



(wherein X represents a halogen or a hydrogen atom, $R^1$ and $R^2$ concurrently or differently represent a hydrogen atom or a C1 to C6 alkyl group, or $R^1$ and $R^2$ together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 6] The agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy, according to claim 5, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

【書類名】　手続補正書
【整理番号】　Ｐ０６０２３ＳＫＫ
【提出日】　平成１９年８月３日
【あて先】　特許庁長官　殿
【事件の表示】
　【出願番号】　特願２００５－５１７５０２
【補正をする者】
　【識別番号】　０００１４４５７７
　【氏名又は名称】　株式会社　三和化学研究所
【代理人】
　【識別番号】　１００１０８２８０
　【弁理士】
　【氏名又は名称】　小林　洋平
　【電話番号】　０５４９－２７－５５１５
【発送番号】　３４８１８８
【手続補正１】
　【補正対象書類名】　特許請求の範囲
　【補正対象項目名】　全文
　【補正方法】　変更
　【補正の内容】
【書類名】　特許請求の範囲
　【請求項１】一般式
【化１】

II(b)(iii)



（式中Ｘはハロゲン又は水素原子を意味し、$R^1$および$R^2$は、同時にあるいは別々に、水素原子、C1-6アルキル基を示すか、又は、$R^1$と$R^2$は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に５～６員の複素環を示す。）

で示される化合物を有効成分とする、糖尿病黄斑症の予防又は治療剤。

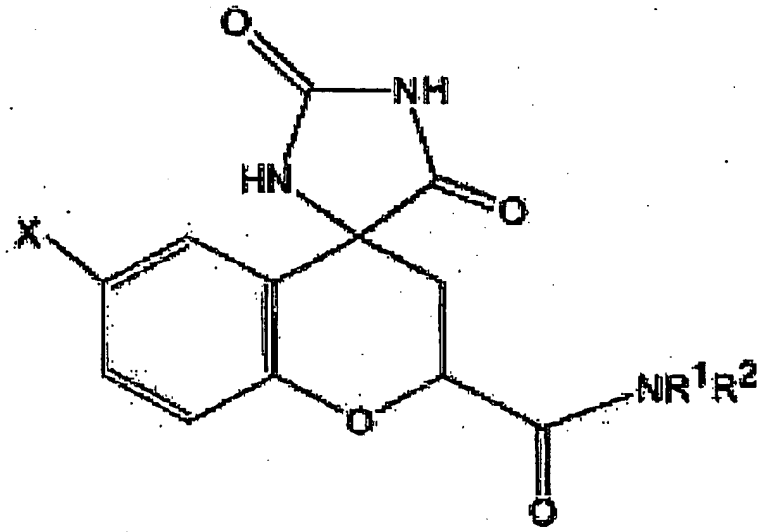
【請求項２】　化合物が(２Ｓ,４Ｓ)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項１に記載の糖尿病黄斑症の予防又は治療剤。

【請求項３】　糖尿病黄斑症における黄斑浮腫又は糖尿病色素上皮症に使用される、請求項１又は２に記載の糖尿病黄斑症の予防又は治療剤。

【請求項４】　糖尿病黄斑症における視力の改善又は低下防止剤として使用される、請求項１又は２に記載の糖尿病黄斑症の予防又は治療剤。

【請求項５】　一般式

【化２】




（式中Ｘはハロゲン又は水素原子を意味し、$R^1$および$R^2$は、同時にあるいは別々に、水素原子、C1-6アルキル基を示すか、又は、$R^1$と$R^2$は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に５～６員の複素環を示す。）

で示される化合物を有効成分とする、糖尿病黄斑症における視力の改善又は低下防止剤。

【請求項６】　化合物が(２Ｓ,４Ｓ)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項５に記載の糖尿病黄斑症における視力の改善又は低下防止剤。

# Decision to Grant a Patent

Application number: Application for patent 2005-517502
Date of Drafting: Heisei 19(2007) August 27
Patent examiner: TOMA, Hirofumi 3543 4C00
Title of invention: Prevention or the medical treatment agent of diabetic maculopathy
The number of claims: 6
Applicant: SANWA KAGAKU KENKYUSHO CO. LTD.
Representative: KOBAYASHI, Youhei

About this application, since no Reason for refusal is found, a Decision to Grant a Patent is carried out.

Director General(p.p.) Director(p.p.) Examiner Assistant examiner Manager for Determination of Classification OHTAKU, Ikuji TOMA, Hirofumi TSURUMI, Hidenori 8829 3543 8415

1. Distinction of Patent: Usually
2. Reference documents: **
3. Application of Patent Law, Section 30: Nothing
4. Change of Title of Invention: Nothing
5. International Patent Classification (IPC)

C07D491/107 , A61K 31/4166 , A61P 3/10 , A61P 27/02

6. Deposition of Microorganism

7. Display of Purport that Retroactivity of Filing Date is not Accepted

Decision to Grant a Patent(Memorandum)

Application number: Application for patent 2005-517502

1. Technical Fields to Be Searched (IPC, DB Name)
C07D 491/107 A61K 31/33-33/44A61P 27/02 A61P 3/10 CAplus(STN)CAOLD(STN) REGISTRY(STN)MEDLINE(STN)BIOSIS(STN)EMBASE(STN)WPIDS(STN)

2. Reference patent documents
JP,07-242547,A (JP, A)

3. Reference books and magazines
SPEICHER, M.A.et al., and Expert Opinion on Emerging Drugs, 2003, Vol.8/No.1 and p.239-250AKITA, M.et al., Acta.Med.Okayama, 1993, and Vol.47/No.5 and p.299-304GIANNOUKAKIS, N. -- [ Current Opinion in ] Investigational Drugs, 2003, Vol.4/No.10 and p.1233-1239FERRIS, III, F.L., Survey of Ophthalmology, 2002, Vol.47/Suppl.2, p.S237

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[Translation done.]

(English translation)
Reference: Dispatch No. 348188 Dispatch Date:05/09/2007

**NOTIFICATION OF ALLOWANCE**

| | |
|---|---|
| Patent Application No. | Patent Application No. 2005-517502 |
| Drafting Date | 27th August 2007 |
| Examiner of JPO | Hirofumi TOUMA, Serial No. 3543-4C00 |
| Title of the Invention | PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY |
| Number of Claims | 6 |
| Patent Applicant | SANWA KAGAKU KENKYUSHO CO., LTD. |
| Representative of Applicant | Yohei KOBAYASHI |

This application is decided to be allowed since no reason for refusal has been found.

It is attested that the foregoing is the same as recorded on the file.
Date of attestation: 29th August 2007
Administrative Official of Ministry of Economy, Trade and Industry, Emiko HIRASE

Note: The patent fee must be paid within 30 days upon receipt of this communication.

整理番号: 発送番号:436492 発送日:平成19年 9月 5日 1/E

# 特許査定

| | |
|---|---|
| 特許出願の番号 | 特願２００５－５１７５０２ |
| 起案日 | 平成１９年 ８月２７日 |
| 特許庁審査官 | 當麻 博文 ３５４３ ４Ｃ００ |
| 発明の名称 | 糖尿病黄斑症の予防又は治療剤 |
| 請求項の数 | ６ |
| 特許出願人 | 株式会社三和化学研究所 |
| 代理人 | 小林 洋平 |

この出願については、拒絶の理由を発見しないから、特許査定をします。

---

上記はファイルに記録されている事項と相違ないことを認証する。
認証日 平成19年 8月29日 経済産業事務官 平瀬 恵美子

注意：この書面を受け取った日から３０日以内に特許料の納付が必要です。

I(a)(ii)

**Practitioner's Docket No.: 868_012** ***PATENT***

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

Ser. No.: 10/587,320 Art Unit: 4173

Filed: May 10, 2007 Examiner: Nissa M. Westerberg

Confirmation No.: 4731

For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

Sir:

Enclosed are copies of References AC through AL which were previously cited in an Information Disclosure Statement filed July 26, 2006.

Pursuant to 37 CFR §1.56, the attention of the Patent and Trademark Office is hereby directed to newly cited non-patent literature References AM and AN as listed on the attached Form PTO-1449. Required copies of these references are also attached.

The above information is presented so that the Patent and Trademark Office may, in the first instance, determine any materiality thereof to the claimed invention. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that these references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

December 18, 2007
Date

Stephen P. Burr
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| Form PTO-1449<br>US DEPARTMENT OF COMMERCE<br>PATENT AND TRADEMARK OFFICE<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>*(use as many sheets as necessary)* | | | | *Complete if Known* | |
|---|---|---|---|---|---|
| | | | | Application Number | 10/587,320 |
| | | | | Filing Date | May 10, 2007 |
| | | | | First Named Inventor | Noriaki KATO |
| | | | | Art Unit | 4173 |
| | | | | Examiner Name | Nissa M. Westerberg |
| | | | | Confirmation No. | 4731 |
| Sheet | 1 | of | 1 | Attorney Docket No. | 868_012 |

**U.S. PATENT DOCUMENTS**

| Exam Initial | | Document Number | Date | Name | Our Docket No. | Class | Sub Class | Filing Date |
|---|---|---|---|---|---|---|---|---|
| | *AA* | 6,479,729 | 11-12-2002 | Campochiaro et al. | | | | |
| | *AB* | 4,740,517 | 04-26-1988 | Kurono et al. | | | | |

**FOREIGN PATENT DOCUMENTS**

| | | Document Number | Date | Country | Class | Sub Class | Translation | Abstract |
|---|---|---|---|---|---|---|---|---|
| | *AC* | 07-242547 A1 | 09-19-1995 | JP | | | | |
| | *AD* | 61-200991 A1 | 09-10-1986 | JP | | | | |
| | *AE* | 03-072226 B2 | 11-18-1991 | JP | | | | |
| | *AF* | 08-231549 A1 | 09-10-1996 | JP | | | | |
| | *AG* | 0 719 556 A2 | 07-03-1996 | EP | | | | |

**OTHER DOCUMENTS**
**(Including Author, Title, Date, Pertinent Pages etc.)**

| | | |
|---|---|---|
| | *AH* | Speicher, Matthew A. et al., *"Pharmacologic Therapy for Diabetic Retinopathy,"* Expert Opinion on Emerging Drugs, Vol. 8, No. 1 (2003), pages 239-250 |
| | *AI* | Masahiko Akita et al., *"Effects of and Aldose Reductase Inhibitor, SNK-860, on the Histopathological Changes of Retinal Tissues in a Streptozotocin-Induced Rat Model,"* Acta Med. Okayama, Vol. 47, No. 5 (1993), pages 299-304 |
| | *AJ* | Irina G. Obrosova et al., *"Aldose Reductase Inhibitor Fidarestat Prevents Retinal Oxidative Stress and Vascular Endothelial Growth Factor Overexpression in Streptozotocin-Diabetic Rats,"* Diabetes, Vol. 52, No. 3 (2003), pages 864 to 871 |
| | *AK* | Giebel, S.J. et al., *"Upregulation of Extracelluar Proteinases and Angiopoietin 2 during Blood-Retinal-Barrier Alteration in the Diabetic Rat Model,"* ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2003, pp. Abstract No. 3903 |
| | *AL* | Sima, J. et al., *"Angiostatin Decrease Vascular Leakage by Down-Regulating VEGF Expression."* ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2003, pp. Abstract No. 363. |
| | *AM* | Nick Giannoukakis, Fidarestat, Sanwa Kagaku/NCCurex/Sankyo, Current Opinion in Investigational Drugs, 2003, Vol. 4, No. 10, pp. 1233-1239. |
| | *AN* | Frederick L. Ferris, III, MD, "Evaluation of New Treatment Paradigms for Diabetic Retinopathy and Macular Edema," Survey of Ophthalmology, Volume 47, Supplement 2, December 2002, p. S237. |

| Examiner: | | Date Considered: | |
|---|---|---|---|

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**Practitioner's Docket No.: 868_012** ***PATENT***

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

Serial No.: 10/587,320 Art Unit: 4173

Filed: May 10, 2007 Examiner: Nissa M. Westerberg

Conf. No.: 4731

For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL PRELIMINARY AMENDMENT**

Sir:

Further to the Preliminary Amendment filed July 26, 2006, Applicants wish to further amend the subject application as follows:

**Amendments to the Claims** are reflected in the listing of claims which begins on page 2 of this paper.

**Remarks/Arguments** begin on page 4 of this paper.

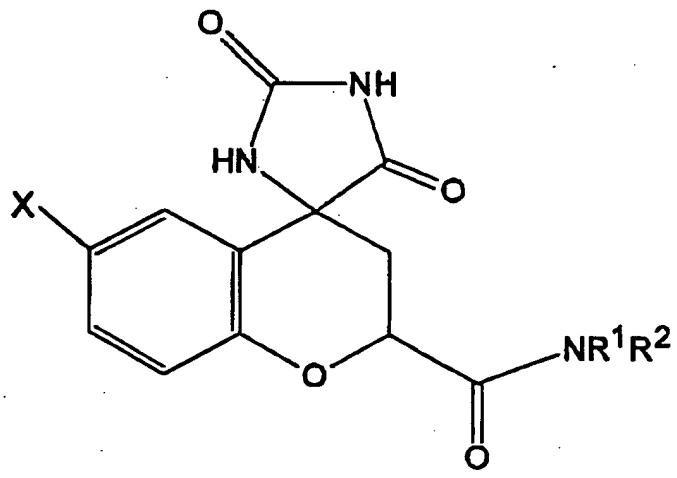
**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claims 1-9 (Cancelled).

10. (Currently Amended) A method for preventing/ameliorating diabetic maculopathy in a mammal comprising administering to the subject an effective amount of a compound represented by the following general formula:




wherein X represents a halogen or a hydrogen atom, $R^1$ and $R^2$ concurrently or differently represent a hydrogen atom or ~~an optionally substituted~~ a C1 to C6 alkyl group, or $R^1$ and $R^2$, together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle.

11. (Previously Presented) The method for preventing/ameliorating diabetic maculopathy according to claim 10, wherein the compound is administered in the form of an oral agent.

12. (Previously Presented) The method for preventing/ameliorating diabetic maculopathy according to claim 10, wherein the compound is (2S, 4S)-6-fluoro-2',5'-dioxospiro [chroman-4,4'-imidazolidine]-2-carboxamide.

13. (Currently Amended) The method for preventing/ameliorating diabetic maculopathy according to claim 10, which is [[used]] for use in treating macular edema or retinal pigment epitheliopathy in diabetic maculopathy.

14. (Currently Amended) The method for preventing/ameliorating diabetic maculopathy according to claim 10, which is [[used]] for use in improving visual acuity or inhibiting a deterioration of visual acuity in diabetic maculopathy.

Claims 15-17 (Cancelled).

## REMARKS/ARGUMENTS

Claims 10-14 are pending herein. Claims 15-17 have been cancelled without prejudice or disclaimer. Claim 10 has been amended to essentially correspond to independent claim 1 that was allowed in the corresponding Japanese National Phase Application (JP 2005-517502). No new matter has been added. Applicants believe the case is now in condition for examination.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, he is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

December 18, 2007
Date

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